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Regional Differences of Hepatitis C Virus Infection in Kentucky

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REGIONAL DIFFERENCES OF HEPATITIS C VIRUS INFECTION IN KENTUCKY

CAPSTONE PROJECT PAPER

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ABSTRACT

Objective: Few studies have been conducted in Kentucky to investigate the statewide prevalence of HCV infection and its associated risk factors. The purpose of this study was to examine the factors related to HCV infection in the state, and specifically to investigate geographical differences of HCV infection between those residing in Appalachian vs. Non-Appalachian counties in Kentucky.

Methods: The study sample (n =5205) was selected from a pool of 8300 high-risk individuals participating in a pilot cross-sectional study on HCV conducted by the Kentucky Department for Public Health. The pilot study involved serologically testing participants for antibodies against HCV infection and having participants complete an interview-administered questionnaire at the same time to examine behavioral and socio-demographic characteristics related to HCV infection. Univariate, bivariate, and logistic regression analyses were carried out using SPSS and maps were produced using ArcGIS software. Frequency distribution, adjusted odds ratios (AORs), and corresponding 95% confidence intervals (95% CIs) were reported.

Results: Of the 5205 participants selected (2241 males, 2964 females; mean age, 30.4 ± 10.5 years); 9.8% tested positive for anti-HCV antibodies. Residence in Appalachian vs. Non-Appalachian Kentucky was not significantly associated with HCV antibody status. In the multivariate analysis, Blacks (AOR: 0.42, 95% CI: 0.26 – 0.66) and men who have sex with men (MSM) (AOR: 0.36, 95% CI: 0.17 – 0.73) were significantly less likely to be HCV positive after adjusting for all other variables. HCV seropositivity was positively associated with age (AOR: 1.03, 95% CI: 1.02 – 1.04), history of injection drug use (IDU) (AOR: 41.27, 95% CI: 31.94 – 53.31), and presence of tattoos (AOR: 1.49,

95% CI: 1.14 – 1.96). Gender was also found to significantly modify the association between residence and HCV antibody status, specifically in the Appalachian region.

Conclusion: This was the first statewide analysis to examine the prevalence of HCV infection among high-risk population residing in Appalachia vs. Non-Appalachian counties in Kentucky. The main variables associated with HCV infection in these regions were age, Black race, history of IDU, MSM and presence of tattoos. Addressing these risky behaviors and particular populations through age- and gender-specific preventive and treatment measures may reduce the high prevalence of HCV infection in the state of Kentucky. However, more research is required to further characterize HCV-related risk factors with respect to residence in Appalachian vs. Non-Appalachian to determine how these measures can be effectively implemented.

Keywords: Hepatitis C virus; Kentucky; injection drug use; Appalachian vs. Non-Appalachian residence

INTRODUCTION

An estimated 1.6%, roughly 4.1 million of the United States (US) population is affected by Hepatitis C virus (HCV) infection (Armstrong et al., 2006; Kramer et al., 2010). Approximately 80% of this population is chronically infected with HCV, which equates to over 3.2 million people (Armstrong et al., 2006); three-quarters of whom were born during 1945 through 1965 (CDC, 2015). National surveillance data from 2013 indicate an incidence rate of 0.7 cases per 100,000 in the US (CDC, 2015). The highest incidence was observed among people 20 to 29 years of age (CDC, 2015). In 2013, 19,368 deaths were attributed to HCV-related events in the US (CDC, 2015).

Approximately three-quarters of people infected with HCV are asymptomatic (CDC, 2015). Symptoms, if present, are nonspecific. The acute phase of HCV infection, which is defined by laboratory confirmation, is short-term and those infected present either with no symptoms or mild symptoms including jaundice and/or elevated alanine aminotransferase greater than 400 IU/L (Suryaprasad, 2014). Of those infected, over 40-50% recover spontaneously and the rest progress into a chronic phase of the infection. Untreated HCV infection persists for 20-30 years resulting in advanced liver disease (Zignego et al., 2012). This includes liver fibrosis, cirrhosis, liver failure, and ultimately hepatocellular carcinoma (El-Serag and Mason, 2000; Thomas and Seeff, 2005). Currently, HCV is the most common cause of chronic liver disease and leading cause of liver transplantation in the US (Alter, 2007; Gordon et al., 2009; Rustgi, 2007; Searson et al., 2014).

The predominant route of HCV transmission in the US is percutaneous exposure to contaminated blood and other blood products. Populations identified at risk for HCV infection include injection drug users (IDU) and occupational exposure to blood via

needlestick injuries, those undergoing invasive medical procedures, the homeless population, men who have sex with men (MSM), those with human immunodeficiency virus (HIV), inmates in correctional facilities, persons born between 1945 and 1965, and people who misused alcohol (Alter, 2007; CDC, 2015; Missiha et al., 2008; Searson et al., 2014). HCV infection is not efficiently transmitted via sex. However, engaging in rough sex, sex with multiple sexual partners, and engaging in high-risk sexual practices such as unprotected anal sex among MSM, are associated with increased risk of HCV infection (CDC, 2015; McFaul et al., 2014).

The implementation of universal precautions to prevent transmission of blood-borne infections by different establishments including hospitals has resulted in a progressive decline in the incidence of acute HCV infection in the US (CDC 2015; CDC, 1988). Yet, state surveillance data reports from 2006-2012 obtained from NNDSS (2014) revealed significant increases in cases of acute HCV infection for Kentucky, Tennessee, Virginia, and West Virginia. In 2012, these three states accounted for an estimated 20.4% of acute HCV cases reported, with 4.1 cases per 100,000 reported in Kentucky alone compared to the national rate of 0.7 cases per 100,000 (CDC, 2015). These data show a drastic increase of acute HCV infection in Kentucky to 4.1 cases per 100,000 from 0.7 cases per 100,000 reported by the state in 2007 (CDC, 2015). Notably, many Kentuckians are likely unaware of their HCV infection status due to most infections being asymptomatic as well as the lack of available resources for screening and testing high-risk individuals throughout the state.

Previous studies have focused on assessing the association between several risk factors and HCV infection mostly in rural Appalachian regions in Kentucky. The rate of HCV infection in Appalachian Kentucky has been found to be strongly associated with

IDU (Christian et al., 2010). According to Havens and colleagues (2013) the prevalence of HCV infection among people who inject drugs (PWID) in Appalachian Kentucky was estimated at 54.6%, which was similar to results from other smaller studies in the region (Christian et al., 2010) and national data (Armstrong et al., 2006). Havens and colleagues (2013) also identified several factors associated with HCV infection including herpes simplex virus 2 (HSV-2), injection of cocaine, injection of prescription opioids, injecting for at least 5 years, posttraumatic stress disorder, and recent sharing of syringes. These risk factors such as injecting drugs have also been associated with active HCV infection (HCV RNA positivity) (Young et al., 2012).

Research has shown than the high rates of HCV infection can be observed in young PWID, predominantly White adults, residing in or near Appalachian jurisdictions (Suryaprasad et al., 2014). This study demonstrated that the incidence of acute HCV infection in the US was highest in those less than 30 years of age residing in rural areas east of the Mississippi River in five states, among which, Kentucky had the highest rate. Results from Suryaprasad and colleagues (2014), and Zibbell and colleagues (2015) indicated the rates of HCV infection to be more than double amongst young PWID less than 30 years of age, residing in or near Appalachian regions compared to young PWID residing in Non-Appalachian urban areas.

This study seeks to further explore the Appalachian vs. Non-Appalachian disparities in the epidemiology of HCV infection. The study utilized data obtained from the first statewide study ever conducted in Kentucky to assess the risk factors associated with HCV infection. The purpose of this study was to examine the risk factors related to HCV infection in Kentucky, and specifically to test the hypothesis that HCV infection

would be more prevalent among residents of Appalachian Kentucky compared to those residing in Non-Appalachian Kentucky.

MATERIALS AND METHODS

Study Design and Population

The Kentucky Adult Viral Hepatitis Prevention Coordinator (KY-AVHPC) established the Kentucky Viral Hepatitis Coalition, a multidisciplinary team that includes Kentucky Department for Public Health (KDPH) staff, infection preventionists, and regional epidemiologists from local health departments, substance abuse treatment center program managers, KY Department of Corrections medical director, Kentucky Primary Care Association director, primary care providers and networks, and hepatologists and infectious disease specialists for the treatment of viral hepatitis in Lexington and Louisville.

Kentucky received permission in April 2012 to conduct a pilot laboratory testing project for HCV infection in 37 selected local health departments (LHD) jurisdictions. LHDs were given guidelines for screening and obtaining blood samples from high-risk individuals for HCV antibody and RNA testing to determine those exposed to HCV infection. Data was also administered through interview-administered questionnaires. The eligibility criteria for the pilot study included being at least 18 years of age, a resident of Kentucky, history of IDU, lifetime history of multiple sexual partners, or lifetime history of STD. Patients presenting with active liver disease of any cause were excluded from the

study. This pilot project lasted from May 1, 2012 to October 31, 2014. This compiled data were reported to the Viral Coordinator at KDPH.

By the end of the study, 8300 high-risk individuals underwent interview-administered questionnaires and had blood samples drawn at the same time at different substance abuse clinics, STD clinics, rehabilitation centers, and other treatment centers within local health departments. The dried blood sample specimens collected by finger stick were submitted to the Kentucky State Public Health Laboratory for analysis. This analysis focused on screening the participants for the presence of anti-HCV antibodies using an enzyme immunoassay (EIA) test (sensitivity: 91.8%; specificity 98.2%) (Chernesky et al., 2001). Blood specimens from those with anti-HCV antibodies were referred to one of two national reference laboratories (Quest Diagnostics or LabCorp – KY) to carry out the HCV RNA confirmatory test using the recombinant immunoblot assay (RIBA) test from May 2012 to mid-June 2013 and the quantitative real-time polymerase chain reaction (PCR) RNA test from mid-June 2013 to October 2014. During the transition from RIBA to PCR testing, RNA testing was not performed for an unknown number of HCV antibody positive specimens, and also the sensitivity and specificity differed between the RIBA and PCR tests; thus, limiting reliable aggregation of the results. Therefore, RNA results were excluded from this analysis.

At the start of the pilot study, the KDPH did not have a Viral Hepatitis Coordinator employed to receive the completed questionnaires and test results. In addition, the State Laboratory could store data for only 6 months. As a result, most of the initial data collected in the first 6 months of the pilot study were lost. By the end of the study, the total compiled data at KDPH included 5300 completed questionnaires and test results. Of the 5300, 29

were tests performed on individuals who resided outside of Kentucky and 66 surveys were missing responses from all the behavioral survey questions and part of the demographic survey questions. Thus, these were excluded from analysis, leaving a final sample size of 5205.

Questionnaire Survey and Data Collection

The interviewer-administered questionnaires were developed by the KDPH, based on knowledge of potential risk factors associated with HCV infection and with the guidance and advice from regulatory officials and viral hepatitis coordinators working in other states. A trained staff member at each center or local health department interviewed the high-risk individuals using the questionnaire to obtain information on socio-demographics (age, gender, race, ethnicity, and home address zip code), risk behavior (MSM, lifetime history of multiple sexual partners, history of IDU, and presence of tattoos), and medical history (HIV status and lifetime history of STD). The hard copy completed surveys were sent to the Viral Hepatitis Coordinator at the KDPH. This information and test results were compiled in Microsoft Excel 2013 software.

Statistical Analysis

SPSS, version 22 (IBM Corp) were used for the analysis and ArcGIS mapping software was used to create maps. Descriptive statistics were reported as frequency and percentages for categorical variables; and as means and standard deviations for continuous variables. The only continuous variable in this study was age. The categorical variables included gender, race, ethnicity, history of IDU, lifetime history of multiple sex partners,

MSM, lifetime history of STD, presence of tattoos, self-reported HIV status, and residence in an Appalachian or Non-Appalachian county. Residential address zip codes were used to determine whether or not participants resided in a county designated by the Appalachian Regional Commission to be in an Appalachian region versus Non-Appalachian region (ARC, 2015). The HCV prevalence by county was graphically represented in Figure 1.

Univariate and bivariate descriptive analyses were conducted to assess the association between each independent variable (described above) with the outcome of interest (HCV antibody status). Descriptive statistics are presented by HCV antibody status in Table I. Logistic regression analysis was carried out to compute the crude odds ratio and 95% confidence interval for the variables. Statistical significance was determined using criteria of p-value <0.05. This is presented in Table I.

The next steps in the analysis used modeling to examine the association between residence in Appalachian vs. Non-Appalachian counties and HCV antibody status. A summary of the statistical analyses is also found under the Appendix section.

Collinearity assessment. All the variables were put into a linear model to compute tolerance and variance inflation factor (VIF) to assess for collinearity. Collinearity would be present with a VIF >10 and Tolerance <0.10 (Belsley et al., 2005).

Interaction assessment. Cross-tabulation for each variable by HCV antibody status and residence in Appalachian vs. Non-Appalachian county was carried out to identify strata with cell sizes too small (i.e. cell sizes of zero) to be analyzed in interaction terms reliably. The variables with zero cells were excluded when assessing for interaction. Logistic regression analysis was carried out to compute the odds ratio (OR) for each interaction term's association with HCV antibody status, adjusted for lower-order terms. If the

statistical significance using p-value <0.05 was found, the interaction term was kept for the final model.

Confounding assessment. All of the independent variables were assessed for confounding using a 15% change criteria (Bursac et al., 2008) between the estimated crude odds ratio obtained from the stated association (residence and HCV antibody status) and the adjusted odds ratio obtained after adjusting for each variable as a potential confounder. If the difference between the two measures of association was 15% or greater, then the variable was considered a confounder and kept for the final model.

Multivariable analysis. The first multivariable logistic regression model included the exposure variable (residence in Appalachia vs. Non-Appalachian region), all confounding variables, interaction terms and their lower order terms, and the remaining independent variables that were significantly associated with HCV seropositivity in the univariate analysis in Table I. All 12 variables were run in a linear regression model to reassess for collinearity using tolerance and VIF values. A final model examining the variables associated with HCV antibody status was determined using backward elimination logistic regression analysis. Backward elimination was used to sequentially remove all variables with the highest p-values above the significant p-value <0.05, leaving only the statistically significant variables in the final model including the confounders and interaction terms. The adjusted odds ratio and 95% confidence intervals were computed for the remaining variables in the final model using multivariable logistic regression. Results are presented in Table II.

Stratified analysis by region of residence. Logistic regression analysis was carried out to assess the variables significantly associated with HCV antibody status in Appalachian and Non-Appalachian counties. This was presented in Table III.

Ethics Statement

This study was approved by the Institutional Review Board of the KDPH (CHFS-IRB-DPH-FY15-26) and the Institutional Review Board of University of Kentucky (15-0290-P3H). Informed consent was obtained from all participants in the initial pilot study.

RESULTS

Univariate and Bivariate Analyses of Socio-demographic and Behavioral Factors

Of the 5205 participants included in the analysis, 509 (9.8%) tested positive for antibodies against HCV and 4696 (90.2%) were negative. Data from this study covered 62 out of the 120 counties in Kentucky, including 17 out of 54 total Appalachian counties and 45 out of 66 total Non-Appalachian counties. In the sample, 209 (4.0%) resided in Appalachian counties and 4996 (96.0%) in Non-Appalachian counties. Of the 509 individuals who tested HCV positive, 28 (5.5%) resided in Appalachian counties and 481 (94.5%) in Non-Appalachian counties. Figure 1 demonstrates that the HCV positive individuals were concentrated in the Northern part of the state, even though the participating counties in the study were scattered throughout the state. A total of 37 out of the 62 participating counties did not report any HCV positive case (grey-colored areas).

The map also demonstrates that many Appalachian and Non-Appalachian counties did not participate in the study (white-colored).

Table 1 describes demographic and behavioral characteristics. The mean age of the HCV positive individuals was 31.9 ± 10.2 years and for HCV negative individuals, 30.2 ± 10.6 years. Approximately 43% of the participants were male. The majority (76%) of the sample was White, 24% Black, and <1% "other" races, which in this study included Asian and Mixed races. The participants in this study were mostly (94%) Non-Hispanic. Overall, 14% reported a history of IDU and they accounted for 78.0% of those testing HCV positive; 5% reported being HIV positive and 10% of those were HCV positive. Interestingly, among MSM in the study (5% of the sample), 2.2% were HCV positive with an odds ratio of 0.44 (95% CI: 0.24-0.80). The variables that were not significantly associated with HCV antibody status included gender (p=0.062), "Other" race (p = 0.152), lifetime history of STD (p = 0.812), and residence in Appalachian vs. Non-Appalachian counties (p = 0.074).

Relationship between Appalachian versus Non-Appalachian Residence and HCV Antibody Seropositivity

Gender was determined to be an effect modifier (interaction term OR: 2.55, 95% CI: 1.11 – 5.88, p-value = 0.028). This indicates that for males in the study, the effect of residing in Appalachian counties on HCV seropositivity is more pronounced than for females residing in Appalachian counties. Results from the confounding assessment (Table VI in Appendix) demonstrated that the strength of the association between residence in Appalachia and HCV antibody status (crude OR: 1.45, 95% CI: 0.97 – 2.19) was decreased

by the presence of two confounding variables: race (AOR: 1.20, 95% CI: 0.79 – 1.81), and HIV status (AOR: 1.22, 95% CI: 0.75 – 1.96). The strength of the association between residence in Appalachia and HCV antibody status was increased by the presence of two confounding variables: history of IDU (AOR: 1.96, 95% CI: 1.14 – 3.37), and history of multiple sexual partners (AOR: 1.70, 95% CI: 1.12 – 2.58). In other words, this indicates that race and HIV status each minimize the association between residence in Appalachian vs. Non-Appalachian and HCV antibody status by biasing the measure of association towards the null, whereas history of IDU and history of multiple sexual partners each exaggerate the association between residence in Appalachian vs. Non-Appalachian counties and HCV antibody status as the effect estimate is biased away from the null.

During backward elimination, history of previous STD was removed first, followed by ethnicity. The final model, presented in Table II, included confounders (listed above), interaction terms and their lower order terms, and other statistically significant variables remaining after backward elimination. Adjusting for all the other variables in the model, significant associations were observed between HCV seropositivity and Black race (AOR: 0.42, 95% CI: 0.26 – 0.66), age (AOR: 1.03, 95% CI: 1.02 – 1.04), history of IDU (AOR: 41.27, 95% CI: 31.94 – 53.31), MSM (AOR: 0.36, 95% CI: 0.17 – 0.73), and presence of tattoos (AOR: 1.49, 95% CI: 1.14 – 1.96). There was no significant association between HCV antibody status and residence in Appalachian vs. Non-Appalachian counties, gender, HIV status, history of multiple sexual partners, and "other" races compared to White race. Interestingly, adjusting for all the variables in the final model, the odds of being HCV positive was lower among MSM compared to non-MSM. In addition, the odds of being HCV positive was lower in the Blacks compared to the Whites.

When models were stratified by residence in Appalachian and Non-Appalachian regions, interesting patterns emerged. Table III displays correlates associated with HCV infection among Appalachian and Non-Appalachian residents. Gender, history of IDU and history of multiple sexual partners were the only factors found to be significantly associated with HCV antibody status among residents in Appalachian counties. However, age, race, ethnicity, HIV status, presence of tattoos, MSM, history of IDU and history of multiple sexual partners were found to be significantly associated with HCV antibody status among residents of Non-Appalachian counties. Of note, none of the independent variables were found to be collinear, as all values for VIF were < 2 and Tolerance were > 35.

DISCUSSION

In this analysis, the association between residence in Appalachian vs. Non-Appalachian counties and HCV antibody status was not statistically significant. However several factors were found to influence the association. Race, history of IDU, HIV status, and history of multiple sexual partners were found to confound the association between residence in Appalachian vs. Non-Appalachian counties and HCV antibody status. In the final model, adjusting for confounders, MSM was associated with decreased odds of HCV infection, whereas presence of tattoos and age were associated with increased odds of HCV infection. Of note, the variables associated with HCV seropositivity differed between the geographic regions of Kentucky. For example, gender was associated with HCV infection among Appalachian residents, with males having higher risk, but not associated with HCV infection among Non-Appalachian residents. Race and MSM were associated with HCV

infection among Non-Appalachian residents, with Black race and MSM having lower risk, but were not associated with HCV infection among Appalachian residents. Age and presence of tattoos were also associated with HCV infection among Non-Appalachian residents, with age and presence of tattoos having higher risk, but were not associated with HCV infection among Appalachian residents. History of IDU was associated with HCV among Appalachian and Non-Appalachian residents, with a slightly higher risk in Appalachian residents compared to Non-Appalachian residents.

Results from the present study (Table II) demonstrated that for every one year increase in age, the odds of HCV infection increased by 1.03, while holding all other variables constant. In this study, the 20-29 age group accounted for the most HCV cases, with 247 (48.5%) out of the total 509 HCV positive individuals. This finding is consistent with previous studies, which have indicated that peak prevalence of HCV infection in the US is observed among people aged 20-29 years of age (CDC, 2015). Of note, when the data in the present study were stratified by gender, the positive association between age and HCV infection was significant among males but not females.

The current study also found that the HCV prevalence was highest among White race. This observation was similar to results obtained from the MMWR by Zibbell and colleagues (2015), whereby non-Hispanic Whites have a greater HCV prevalence compared to non-Hispanic Blacks. Another study had reported an epidemic of HCV infection in the US predominantly among Whites less than 30 years of age, residing in Appalachian counties east of the Mississippi River (Suryaprasad et al., 2014). Compared to the White population in the present study, Blacks residing in Non-Appalachian counties appeared to have a protective effect in being HCV positive.

Gender was found to modify the association between residence in Appalachian vs. Non-Appalachian counties and HCV antibody status. In crude analysis of interaction, the association between being male and HCV positive was higher among Appalachian residents compared to Non-Appalachian residents. Males in Appalachia had nearly three times higher odds of being HCV positive than females, while males in Non-Appalachia did not have significantly higher odds of being HCV positive than females. This difference between males and females influencing the effect of HCV seropositivity can be explained by previous studies that demonstrated that rates of HCV infection differ significantly between gender owing to the different behavioral risks undertaken by men and women. Research has shown that women tend to engage more in sexually-related risk behaviors including having unprotected sex in exchange for money or drugs, whereas men tend to engage in lifetime drug-related risk behaviors including needle sharing, and illicit drug use such as crack cocaine (Butterfield et al., 2003).

IDU is one of the most important risk factors for HCV infection, especially among young PWID (Alter, 2007). The results of this study supported those findings; the odds of being HCV positive among those with a history of IDU was over forty-one times higher than those without a history of IDU, after adjusting for the other variables in the model. In addition, history of IDU was found to be associated with HCV infection among residents in Appalachian and Non-Appalachian counties. These findings were consistent with other studies, which suggested that HCV infection in Appalachian counties is highly associated with PWID (Christian et al., 2010; Havens et al., 2013; Zibbell et al., 2015). Notably, results from Young and colleagues (2013) indicated that turnover in individuals' injection networks (i.e. injecting with different individuals over time) in Appalachian Kentucky

inferred a protective effect of HCV infection. Nonetheless, the increased rates of HCV infections in Kentucky are likely associated with the prescription opioid epidemic among PWID in Appalachia (Havens et al., 2013; Young et al., 2012).

Presence of tattoos as a possible risk factor for HCV infection has been researched in previous studies. Some of these studies have shown an association between tattooing and increased risk of HCV infection in unregulated settings where tattooing needles are reused (Hwang et al., 2006), commercial tattoo parlors (Haley and Fischer, 2001), and among high-risk groups such as incarcerated population where needles are shared and reused (Hwang et al., 2006; Tohme and Holmberg, 2012), whereas other studies have failed to produce a similar association (Hahn et al., 2001). This has been because the tattoo measurement has varied between studies, with some studies distinguishing tattooing from ear piercing and body piercing (Alter, 2002; Hahn et al., 2001; Hwang et al., 2006). Tattoos in the present study were defined as presence of ink markings on the skin. In this study, people who had a tattoo were 1.49 times the odds of having HCV infection compared to those who did not have HCV infection after adjusting for the other variables in the model. Notably, presence of tattoos was found to be significantly associated with HCV infection only in Non-Appalachian counties in the state. However, information on the type and location of the tattoos, as well as the environment and expertise of the person imprinting the tattoos were not examined, but might be worthy of investigation in future studies. Moreso, because this observation has been identified mostly in cross-sectional studies (Alter, 2002; Haley and Fischer, 2001) that do not provide a temporal relationship between tattoo exposure and HCV infection, a true causal relationship cannot be made.

The study analysis showed that MSM have decreased odds of HCV seropositivity, specifically in Non-Appalachian counties. Some studies (Buchbinder et al., 1994; McFaul et al., 2014) have indicated that HCV infection is mostly found among MSM injecting drugs and engaging in sexual activity with multiple partners. There has also been a strong association between HCV infection and HIV-infected MSM (Workowski and Berman, 2010). This protective effect in this study could be due to increased awareness among these population resulting in less people engaging in risk behaviors including IDU and unprotected high-risk sexual practices. More so, this observation could be due to the small MSM population size (n=237) in this study, of which, a smaller fraction of 11 (2.2%) tested positive for anti-HCV antibodies. This small sample size provided a low statistical power to detect the true effect. In addition, because the entire sample was composed of high-risk individuals, the MSM population was being compared to other high-risk groups such as PWID instead of the general population, which would affect its measure of association with HCV infection (i.e. MSM are at lower risk of HCV infection compared to PWID). More research is required to improve understanding of HCV transmission and measures currently undertaken by MSM to reduce HCV infection risk.

Sexual transmission of HCV is uncommon, except among MSM (Workowski and Berman, 2010). The risk of sexual transmission of HCV among monogamous couples has been determined to be extremely rare (Karmochkine et al., 2006; Marian et al., 2003; Rustgi, 2007). Results from Armstrong and colleagues (2006) indicate that having greater than 20 lifetime sexual partners has been significantly associated with HCV seropositivity in the US after controlling for age and sex, as it increases the risk of HCV infection by fourfold. According to results from this study, having a history multiple sexual partners

was not significantly associated with HCV infection in the univariate analysis or in the final model. However, when stratified by the residence in Appalachian vs. Non-Appalachian counties, history of multiple sexual partners was found to be independently associated with HCV infection among residents in both Appalachian and Non-Appalachian counties. This difference could be explained by the fact that adequate data was not available on the number of sexual partners engaging in particular high-risk behaviors (i.e., data were only available on whether or not they had multiple partners, not *how many* partners and the risk behavior of those partners). Takeuchi and colleagues (2015) had indicated that having HCV-infected sexual partners was significantly associated with HCV seropositivity among men, and not among females. Interestingly, the association between multiple sexual partners and HCV seropositivity in this study was significant only among females and not among men for unknown reasons. Further studies are required to elucidate the association of sexual risk behavior among men and women.

Limitations

The study had several limitations. First, data collected from the surveys was based on self-reported behaviors. This study assumes that the information provided by the participants was accurate and valid. However, self-reported information introduces biases such as recall bias and information bias, specifically misclassification bias that results in residual confounding. Second, being a cross-sectional study, previous exposure history to the different factors does not infer causality of the HCV infection. These factors cannot be said to cause HCV infection over time. Third, the presence of values less than 5 and missing data in some cells in the contingency tables may impact the statistical power to detect

associations during the stratified analysis. Fourth, selection bias may have occurred, given that only high-risk individuals at particular centers were selected as the study population. Fifth, 37 LHD testing sites were invited to participate; only 30 participated in this study, suggesting that the results may not be representative of all counties in the state, especially if the non-participating counties had a high prevalence of HCV infection, thereby affecting the external validity of the study. Lastly, this study used only HCV antibody test results, whereby an HCV antibody positive result meant having been infected with HCV at some point in the past. HCV antibody status provides no information on the active or chronic state of the infection.

Public Health Implications

The results from this study highlight opportunities for public health programs. Of note, many counties did not participate in the cross-sectional study due to lack of resources to carry out the HCV testing and questionnaires. Programs are thereby needed to increase resources in those counties with insufficient resources in order to foster participation in future HCV studies and conduct HCV surveillance. In addition, gender-specific preventive interventions tailored towards particular geographic regions, specifically men in rural Appalachia, can help decrease the prevalence of HCV infection in Kentucky. National health survey data indicate that approximately 50% of HCV-infected persons in the US have been tested for HCV, and that only 6% of those tested receive adequate treatment (Davis et al., 2011; Munir et al., 2010). This demands implementation of primary prevention programs, including education to professional and public institutions, effective screening and risk-reduction counseling of high-risk individuals, referral of care to

substance abuse treatment clinics and hospitals to improve access and increase the proportion of high-risk individuals receiving treatment, as recommended by CDC (1998). Reports from CDC (1998) indicate that secondary prevention measure can reduce the risk of developing the long-term complications of HCV infection by identifying HCV positive people and providing appropriate medical treatment and management. This also requires early placement on the liver transplantation list for those with advanced liver disease.

There is an urgent need to enroll high-risk young adults into substance abuse treatments and treatment facilities. Such undertaking requires collaboration between federal organizations such as CDC, working with the state and local health departments to implement measures to address the parenteral prescription drugs epidemic and HCV infection. Any intervention to decrease the rates of HCV infection should include educating different age groups on safe sexual practices, targeting different tattoo parlors, and increasing the number of needle exchange programs, which targets the PWID. Alter (2002) had indicated that an effective prevention measure to reduce HCV infection among PWID would be to nullify the restrictive paraphernalia regulation and increase the number of needle exchange programs whereby sterile syringes and needles can be made available to this population. Implementation of needle exchange programs has also be shown to be effective not only in reducing transmission of HCV infection, but also HCV incidence in PWID (Des Jarlais et al., 2009; Van Den Berg et al., 2007). Recently, the anti-heroin legislation (Senate Bill 192) was passed in Kentucky allowing health departments in the state of Kentucky to establish needle exchange programs where people who use drugs can exchange their used needles and syringes for clean ones, and also for the state to increase access to treatment for this population (Cheves, 2015; Wynn, 2015).

CONCLUSION

In conclusion, this study showed that age and MSM, history of IDU and presence of tattoos influenced the association between residence in Appalachia vs. Non-Appalachia and HCV infection in the state of Kentucky. Furthermore, risk factors differ between the geographic regions of Kentucky. Therefore, reinforced public education and intervention targeting different gender groups and risky behaviors are required to prevent HCV infection in the state. Despite the limitations of this study, information was provided on some risk factors associated with the high prevalence of HCV infection in Kentucky and the study also highlighted the distribution of HCV infection and its significant associated variables depending on the region of residence. More research is required to provide a better understanding of the association between these risky behaviors and HCV infection.

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TABLES AND FIGURES

Table I. Descriptive and Bivariate Analyses of Factors Associated with HCV Antibody Status

Risk factors	Total (n=5205)	Anti-HCV Positive (n=509)	Anti-HCV Negative (n=4696)	Unadjusted OR (95% CI)	*P*-value
	N (%)	N (%)	N (%)		
Gender					
Female	2964 (56.9)	270 (53.0)	2694 (57.4)	*reference*	–
Male	2241 (43.1)	239 (47.0)	2002 (42.6)	1.19 (0.99-1.43)	0.062
Race					
White	3952 (75.9)	481 (94.5)	3471 (73.9)	*reference*	–
Black	1221 (23.5)	27 (5.3)	1194 (25.4)	0.16 (0.11-0.24)	0.000
Others[a]	32 (0.6)	1 (0.2)	31 (0.7)	0.23 (0.03-1.71)	0.152
Ethnicity					
Hispanic	297 (5.7)	6 (1.2)	291 (6.2)	*reference*	–
Non-Hispanic	4908 (94.3)	503 (98.8)	4405 (93.8)	5.54 (2.46-12.49)	0.000
Age (years), mean (SD)	30.4 (10.5)	31.9 (10.2)	30.2 (10.6)	1.02 (1.01-1.02)	0.000
Hx of IDU					
No	4487 (86.2)	112 (22.0)	4375 (93.2)	*reference*	–
Yes	718 (13.8)	397 (78.0)	321 (6.8)	48.31 (38.07-61.32)	0.000
HIV Status					
Negative	4740 (91.1)	430 (84.5)	4310 (91.8)	*reference*	–
Positive	276 (5.3)	51 (10.0)	225 (4.8)	2.27 (1.65-3.13)	0.000
Unaware[b]	189 (3.6)	28 (5.5)	161 (3.4)	1.74 (1.15-2.64)	0.008
Hx Multiple sexual partners					
No	1086 (20.9)	67 (13.2)	1019 (21.7)	*reference*	–
Yes	4119 (79.1)	442 (86.8)	3677 (78.3)	1.83 (1.40-2.39)	0.000
MSM[c]					
No	4957 (95.2)	498 (97.8)	4459 (95.0)	*reference*	–
Yes	237 (4.6)	11 (2.2)	226 (4.8)	0.44 (0.24-0.80)	0.008
Tattoos[d]					
No	2057 (39.5)	121 (23.8)	1936 (41.2)	*reference*	–
Yes	3078 (59.1)	381 (74.8)	2697 (57.4)	2.26 (1.83-2.80)	0.000
Previous STD[c]					–
No	2925 (56.2)	283 (55.6)	2642 (56.3)	*reference*	0.812
Yes	2269 (43.6)	224 (44.0)	2045 (43.5)	1.02 (0.85-1.23)	
Regional Residence					
Non-Appalachian	4996 (96.0)	481 (94.5)	4515 (96.1)	*reference*	–
Appalachian	209 (4.0)	28 (5.5)	181 (3.9)	1.45 (0.97-2.19)	0.074

SD =standard deviation, Hx = history, IDU = injection drug use, MSM = men who have sex with men, STD= sexually transmitted diseases, KY = Kentucky, 95% CI = 95% confidence interval

[a] Others include Asian and mixed race

[b] Participants either did not know their status or that information was missing

[c] 11 participants had missing data for these variables

[d] 70 participants had missing data for this variable

Table II. Final Multivariate Logistic Regression Model Examining Variables Associated with HCV Antibody Seropositivity

Variables	Adjusted OR	95% Confidence Interval (CI)	*P*-value
Regional Residence			
Non-Appalachian	*reference*	–	–
Appalachian	1.16	0.52-2.62	0.713
Gender			
Female	*reference*	–	–
Male	1.16	0.90-1.48	0.254
Race			
White	*reference*	–	–
Black	0.42	0.26-0.66	0.000*
Others[a]	0.69	0.08-6.37	0.744
Age (years)	1.03	1.02-1.04	0.000*
Hx of IDU			
No	*reference*	–	–
Yes	41.27	31.94-53.31	0.000*
HIV Status			
Negative	*reference*	–	–
Positive	1.37	0.89-2.11	0.153
Unaware[b]	0.99	0.50-1.95	0.977
Hx Multiple sexual partners			
No	*reference*	–	–
Yes	1.31	0.94-1.83	0.110
MSM[c]			
No	*reference*	–	–
Yes	0.36	0.17-0.73	0.005*
Tattoos[d]			
No	*reference*	–	–
Yes	1.49	1.14-1.96	0.004*
Appalachian*Gender	2.52	0.78-8.19	0.124

Likelihood Ratio Chi-Square = 1360.076, on 12 *df*; p-value = 0.000

SD = standard deviation, Hx= history, IDU= injection drug use, MSM= men who have sex with men

*Indicates statistical significance (p<0.05)

[a] Others include Asian and mixed race

[b] Participants either did not know their status or that information was missing

[c] 11 participants had missing data for this variable

[d] 70 participants had missing data for this variable

Table III. Variables Associated with HCV Antibody Seropositivity Stratified by Appalachian and Non-Appalachian Residence

Variables	Appalachian (n=209)		Non-Appalachian (n=4996)	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Gender				
Female	*reference*	–	*reference*	–
Male	2.94 (1.30-6.62)	0.009	1.15 (0.95-1.39)	0.147
Race				
White	*reference*	–	*reference*	–
Black	0.00 (0.00)	0.999	0.17 (0.11-0.25)	0.000
Others[a]	–	–	0.24 (0.03-1.73)	0.155
Ethnicity				
Hispanic	*reference*	–	*reference*	–
Non-Hispanic	–	–	5.45 (2.42-12.31)	0.000
Age (years)	1.00 (0.96-1.04)	0.904	1.02 (1.01-1.02)	0.000
Hx of IDU				
No	*reference*	–	*reference*	–
Yes	54.06 (18.29-159.80)	0.000	48.67 (38.07-62.21)	0.000
HIV Status				
Negative	*reference*	–	*reference*	–
Positive	2.97 (0.28-31.06)	0.363	2.26 (1.64-3.13)	0.000
Unaware[b]	1.78 (0.78-4.06)	0.169	1.49 (0.81-2.75)	0.204
Hx Multiple sexual partners				
No	*reference*	–	*reference*	–
Yes	2.97 (1.20-7.32)	0.018	1.82 (1.37-2.41)	0.000
MSM[c]				
No	*reference*	–	*reference*	–
Yes	2.20 (0.22-21.90)	0.502	0.41 (0.22-0.77)	0.006
Tattoos[d]				
No	*reference*	–	*reference*	–
Yes	2.05 (0.86-4.89)	0.104	2.29 (1.84-2.86)	0.000
Previous STD[c]				
No	*reference*	–	*reference*	–
Yes	1.45 (0.63-3.36)	0.381	1.01 (0.84-1.22)	0.916

OR = odds ratio, SD =standard deviation, Hx = history, IDU = injection drug use, MSM = men who have sex with men, STD= sexually transmitted diseases, KY = Kentucky, 95% CI = 95% confidence interval

[a] Others include Asian and mixed race

[b] Participants either did not know their status or that information was missing

[c] 11 participants had missing data for these variables

[d] 70 participants had missing data for this variable

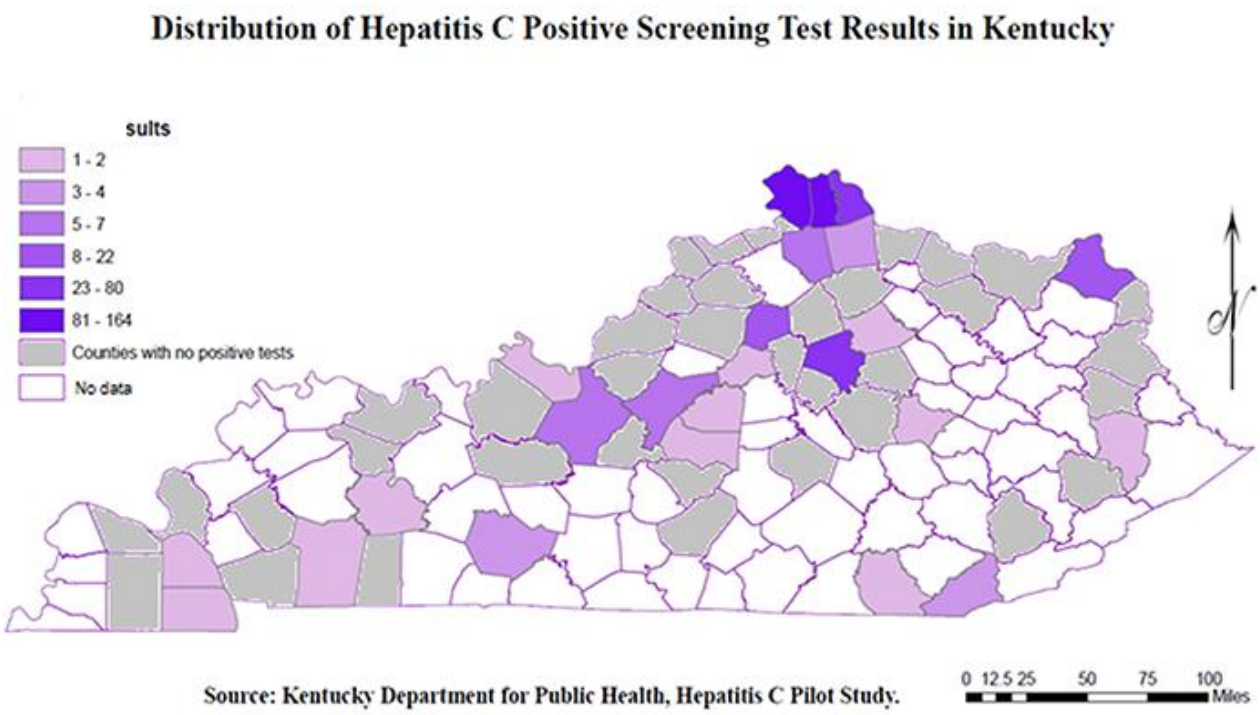

Figure 1. Distribution of HCV positive individuals by county in Kentucky, 2012-2014 (n=5205). The different shades of purple indicate the counties with HCV positive individuals in increasing numbers. The counties with the highest HCV prevalence are concentrated in Northern Kentucky. The gray-colored regions include counties that participated in the statewide survey study but reported no HCV positive individuals. The white-colored counties include those counties that did not participate in the statewide study.

APPENDIX

Table IV. Distribution of Variables between Appalachian versus Non-Appalachian County Residence: Results of Bivariate Analysis

Variables	Appalachian (n=209)		Non-Appalachian (n=4996)	
	HCV+, N (%)	HCV-, N (%)	HCV+, N (%)	HCV-, N (%)
Gender				
Female	14 (50.0)	135 (74.6)	256 (53.2)	2559 (56.7)
Male	14 (50.0)	46 (25.4)	225 (46.8)	1956 (43.3)
Race				
White	28 (100.0)	168 (92.8)	453 (94.2)	3303 (73.2)
Black	0 (0.0)	13 (7.2)	27 (5.6)	1181 (26.2)
Others[a]	0 (0.0)	0 (0.0)	1 (0.2)	31 (0.7)
Ethnicity				
Hispanic	0 (0.0)	0 (0.0)	6 (1.2)	291 (6.4)
Non-Hispanic	28 (100.0)	181 (100.0)	475 (98.8)	4224 (93.6)
Age (years), mean (SD)	30.0 (6.0)	30.0 (11.0)	32.0 (10.0)	30.0 (11.0)
Hx of IDU				
No	8 (28.6)	173 (95.6)	104 (21.6)	4202 (93.1)
Yes	20 (71.4)	8 (4.4)	377 (78.4)	313 (6.9)
HIV Status				
Negative	11 (39.3)	98 (54.1)	419 (87.1)	4212 (93.3)
Positive	1 (3.6)	3 (1.7)	50 (10.4)	222 (4.9)
Unaware[b]	16 (57.1)	80 (44.2)	12 (2.5)	81 (1.8)
Hx Multiple sexual partners				
No	7 (25.0)	90 (49.7)	60 (12.5)	929 (20.6)
Yes	21 (75.0)	91 (50.3)	421 (87.5)	3586 (79.4)
MSM[c]				
No	27 (96.4)	178 (98.3)	471 (97.9)	4281 (95.0)
Yes	1 (3.6)	3 (1.7)	10 (2.1)	223 (5.0)
Tattoos[d]				
No	9 (36.0)	97 (53.6)	112 (23.5)	1839 (41.3)
Yes	16 (64.0)	84 (46.4)	365 (76.5)	2613 (58.7)
Previous STD[c]				
No	15 (57.7)	119 (66.5)	268 (55.7)	2523 (56.0)
Yes	11 (42.3)	60 (33.5)	213 (44.3)	1985 (44.0)

SD =standard deviation, Hx = history, IDU = injection drug use, MSM = men who have sex with men, STD= sexually transmitted diseases, KY = Kentucky

[a] Others include Asian and Mixed race

[b] Participants either did not know their status or that information was missing

[c] 11 participants had missing data for these variables

[d] 70 participants had missing data for this variable

Table V. Assessing Interaction in the Association between Appalachian versus Non-Appalachian Residence and HCV Antibody Seropositivity: Results of Bivariate Analysis

Variables[a]	OR	95% CI	P-value
Appalachian[e]	1.45	0.97-2.19	0.074
Appalachian*Gender	2.55	1.11-5.88	0.028*
Appalachian*Age (years)	0.98	0.95-1.02	0.371
Appalachian*Hx of IDU	1.11	0.37-3.38	0.853
Appalachian*HIV status [b]	0.85	0.54-1.35	0.495
Appalachian*Hx Multiple sexual partners	1.63	0.63-4.20	0.310
Appalachian*MSM[c]	5.39	0.50-58.65	0.166
Appalachian*Tattoos[d]	0.90	0.37-2.19	0.808
Appalachian*Previous STD[c]	1.44	0.61-3.40	0.405

Hx = history, IDU = injection drug use, MSM = men who have sex with men, STD= sexually transmitted diseases, OR = odds ratio, 95% CI = 95% confidence interval
*Interaction present
[a] Race and ethnicity variables were excluded because they contained stratified cell sizes too small (i.e. cell sizes of zero) to be analyzed in interaction terms
[b] 189 participants either did not know their status or that information was missing
[c] 11 participants had missing data for these variables
[d] 70 participants had missing data for this variable
[e] Non-Appalachian residence was the reference group

Table VI. Assessing Confounding in the Association between Appalachian versus Non-Appalachian Residence and HCV Antibody Seropositivity: Results of Bivariate Analysis

Variables	OR[†]	95% CI	P-value
Appalachian[a]	1.45	0.97-2.19	0.074
Appalachian + Gender	1.49	0.99-2.25	0.055
Appalachian + Race	1.20*	0.79-1.81	0.391
Appalachian + Ethnicity	1.38	0.91-2.07	0.127
Appalachian + Age (years)	1.47	0.97-2.21	0.067
Appalachian + Hx of IDU	1.96*	1.14-3.37	0.015
Appalachian + HIV status [b]	1.22*	0.75-1.96	0.421
Appalachian + Hx Multiple sexual partners	1.70*	1.12-2.58	0.012
Appalachian + MSM[c]	1.43	0.95-2.15	0.090
Appalachian + Tattoos[d]	1.42	0.92-2.19	0.113
Appalachian + Previous STD[c]	1.37	0.90-2.08	0.149

Hx= history, IDU = injection drug use, MSM= men who have sex with men, STD= sexually transmitted diseases, OR = odds ratio, 95% CI = 95% confidence interval

*Confounding factors present, as indicated in 15% or greater change in AOR
[a] Non-Appalachian residence was the reference group
[b] 189 participants either did not know their status or that information was missing
[c] 11 participants had missing data for these variables
[d] 70 participants had missing data for this variable
[†]Odds ratios are displayed for the association between Appalachian residence and HCV status, adjusting for the variable listed in Column 1, where applicable

Table VII: Socio-demographic Characteristics across Age Groups, 2012-2014

	Tested (n=5205)	**Screened HCV+ (n=509)**	**Screened HCV- (n=4696)**
Characteristics	**N (%)**	**N (%)**	**N (%)**
Age Group (years)			
10-19	459 (8.8)	17 (3.3)	442 (9.4)
20-29	2575 (49.5)	247 (48.5)	2328 (49.6)
30-39	1224 (23.5)	142 (27.9)	1082 (23.0)
40-49	566 (10.9)	60 (11.8)	506 (10.8)
50-59	302 (5.8)	38 (7.5)	264 (5.6)
60-69	68 (1.3)	4 (0.8)	64 (1.4)
70-79	8 (0.2)	1 (0.2)	7 (0.1)
80+	3 (0.1)	0 (0.0)	3 (0.1)

Table VIII. Association between Variables and HCV Infection Stratified by Gender, 2012–2014

Variables	**Male (n=2241)**		**Female (n=2964)**	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**
Age (years)	1.02 (1.01-1.03)	0.005	1.01 (1.00-1.02)	0.058
Hx Multiple sexual partners				
No	*reference*	–	*reference*	–
Yes	1.20 (0.82-1.76)	0.342	2.45 (1.69-3.57)	0.000
Hx of IDU				
No	*reference*	–	*reference*	–
Yes	49.03 (34.41-69.85)	0.000	47.57 (34.45-65.68)	0.000

Hx = history, IDU = injection drug use, OR = odds ratio, 95% CI = 95% confidence interval

BIOGRAPHICAL SKETCH

Yvette Achuo-Egbe earned a Bachelor of Science degree in Chemistry with a Biology Minor from the University of Memphis, in Memphis, Tennessee in August 2007. She went on to complete a Master of Science degree in Biology with a non-thesis project on Zebrafish maturation and carcinogenesis in May 2009 from the University of Memphis, in Memphis, Tennessee. From 2009 through 2014, Ms. Achuo-Egbe earned a Doctor of Medicine degree from the University of Kentucky College of Medicine, in Lexington, Kentucky. Yvette Achuo-Egbe recently completed her Master of Public Health degree with a concentration in Epidemiology from the University of Kentucky College of Public Health. She also became certified in Public Health.

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